Three-dimensional assessment of ultrasound features in women with clomiphene citrate-resistant polycystic ovarian syndrome (PCOS): ovarian stromal volume does not correlate with biochemical indices

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BACKGROUND: Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrine disorder affecting women of reproductive age. The syndrome is characterized by a combination of polycystic ovarian morphology, clinical features and biochemical indices. The objective of this prospective observational study was to investigate the relationship between the total ovarian volume and the ovarian stromal volume, measured using a three-dimensional (3D) ultrasound scan, with biochemical indices of PCOS. METHODS: Twenty-three infertile women (mean age ± SD: 31 ± 3.1 years; range: 26–37) with clomiphene citrate-resistant PCOS were examined. Early follicular phase (days 2–4) serum FSH, LH and testosterone concentrations were measured following a withdrawal bleed. Total ovarian volume, stromal volume, pre-antral follicle (<10 mm) number and total follicular volume were measured by 3D transvaginal ultrasound. RESULTS: Total ovarian volume, follicular volume and follicle number correlated positively with serum FSH and LH, but not testosterone, concentrations. Ovarian stromal volume correlated strongly with total ovarian volume only, but not with serum FSH, LH or testosterone concentrations. CONCLUSIONS: These findings demonstrate an association of the total ovarian volume, pre-antral follicle number and total follicular volume with some of the biochemical indices of PCOS, but no association was observed between ovarian stromal volume and these indices.

Key words: biochemical indices/ovarian stromal volume/polycystic ovarian syndrome/three-dimensional ultrasonography

Introduction

Polycystic ovarian syndrome (PCOS) is one of the commonest endocrinopathies affecting women of reproductive age (Dunaif, 1992). Using laparotomy followed by histological confirmation, Stein and Leventhal were the first to describe the presence of polycystic ovarian morphology together with amenorrhoea, hirsutism and obesity (Stein and Leventhal, 1935). Since then, the association between the presence of typical ovarian morphology and clinical and biochemical indices of PCOS has been confirmed (Franks, 1989). Both serum LH and testosterone levels are elevated, with normal serum FSH levels (Franks, 1995; Homburg, 1996). This peculiar hormonal imbalance correlates positively with adverse fertility and pregnancy outcome (Shoham et al., 1993; Balen et al., 1995).

The advent of ultrasound scanning provides a non-invasive procedure for the assessment of ovarian size, morphology and internal structure, namely follicles and stroma. Swanson et al. were the first to describe the ultrasound ovarian volume enlargement associated with PCOS (Swanson et al., 1981). Adams et al. then refined the ultrasound diagnosis of PCOS, including also follicle number and ovarian stromal characteristics (Adams et al., 1985). The typical polycystic ovarian morphology is defined by the presence of enlarged ovaries containing an increased number of small follicles (2–8 mm) arranged peripherally around a dense echogenic stroma.

The ultrasound finding of polycystic ovaries in the general population is in the order of 17–22% (Polson et al., 1988; Clayton et al., 1992; Cresswell et al., 1997), and in women with anovulation and idiopathic hirsutism is much higher at ~90% (Adams et al., 1986; O’Driscoll et al., 1994).

Although several ultrasound features such as total ovarian volume and stromal hypertrophy (Dewailly et al., 1993) and increased stromal blood flow (Loverro et al., 2001) have been shown to correlate accurately with PCOS, a correlation between the degree of ultrasound morphology changes and the severity of the endocrinopathy in women with PCOS has not been extensively investigated (van der Westhuizen and van der Spuy, 1996).
The advent of sophisticated new systems such as computerized three-dimensional (3D) ultrasound scanning permits visualization of the transverse plane of the pelvis and more accurate measurement of the total ovarian volume and stromal volume. The precision and high degree of reproducibility of ovarian and endometrial volume measurements obtained using this technique have been reported (Kyei-Mensah et al., 1996a,b).

The present prospective observational study was designed to investigate the relationship between the ultrasound features of PCOS, measured more accurately using 3D transvaginal ultrasound scan, with biochemical indices in women with clomiphene citrate (CC)-resistant PCOS.

Materials and methods

Twenty-three consecutive infertile women (mean ± SD age: 31 ± 3.1 years; range: 26–37) with CC-resistant PCOS presenting to the Gynaecological Endocrine Outpatient Clinic at St Mary’s Hospital, London, were recruited to the study.

Since the cycles were anovulatory, a withdrawal bleed was induced with 10 mg oral medroxyprogesterone acetate (Provera®; Pharmacia and Upjohn, Bucks, UK) daily for 5 consecutive days. Serum LH, FSH and testosterone concentrations were determined on day 2–4 of the cycle. LH and FSH concentrations were measured by means of conventional immunoradiometric assay. The intra-assay variation was 3.1% and the inter-assay variation was 11%. Testosterone concentrations were measured by radioimmunoassay. The intra-assay variation was <4% and the inter-assay variation was <11%.

All women had a 3D transvaginal pelvic ultrasound scan on the same day as hormonal measurements were taken, by a single observer, using a high-frequency 7.5 MHz Voluson transvaginal transducer attached to the Combison 580 system (Kretztechnik AG, Zipf, Austria). All ultrasound measurements were taken in real time. Women with ovarian follicles ≥10 mm or any other ovarian cysts or endometriomas were excluded from the study. Polycystic ovarian morphology was diagnosed when there were more than 10 follicles with diameter ≤8 mm arranged peripherally or scattered throughout an echodense core of stroma (Adams et al., 1986; Polson et al., 1988). Total ovarian volume, follicle number and total follicular volume were measured by rotating the transducer crystal through 360° for ~10 sec. During this time, starting from the tissue margin, the outlined contour changes resulting from serial sections using a rollerball cursor were stored sequentially in the computer memory. The ovarian stromal volume was calculated by subtracting the total follicular volume from the total ovarian volume in each case.

Results

All women had a history of menstrual dysfunction including oligoamenorrhoea and anovulatory infertility, resistant to CC. Within 2–7 days after completing the progestational agent course, all patients had a withdrawal bleed. No morphological uterine abnormalities were observed. Mean body mass index was 26.5 ± 1.7 kg/m². Both the ultrasound features and the biochemical indices are shown in Table I.

Total 3D ovarian volume correlated positively with ovarian stromal volume (P < 0.0001), total follicle number (P < 0.0001) and follicular volume (P < 0.0001). No statistically significant correlation was found between ovarian stromal volume and total follicle number or follicular volume.

The relationship between the ultrasound features (total ovarian volume, stromal volume, follicle number and follicular volume) and biochemical indices (FSH, LH and testosterone) is shown in Table II.

Discussion

This study shows that, despite earlier suggestions that stromal volume was the characteristic ultrasound feature for the diagnosis of PCOS (Conway et al., 1989; Dewailly et al., 1993), when 3D ultrasound scan is used there is no correlation between the biochemical indices and ovarian stromal volume in women with CC-resistant anovulatory PCOS. In contrast, the present study demonstrates that the 3D measurements of total ovarian volume, pre-antral follicle number and total pre-antral follicular volume have better correlation with biochemical indices of PCOS then the 3D measurements of ovarian stromal volume.

This is in contrast to the findings of Kyei-Mensah et al., who showed a positive correlation between stromal volume, as measured by 3D ultrasound, with serum androstenedione concentrations, but not with any other endocrine parameter, including testosterone, in infertile women with PCOS (Kyei-Mensah et al., 1998). The hyperandrogenaemia of
PCOS can be demonstrated with the routine measurement of serum testosterone alone and, therefore, androstenedione is not routinely measured in our practice.

Using two-dimensional (2D) ultrasound, Pache et al. reported a statistically significant relationship between follicle number, ovarian volume and stroma echogenicity with serum LH and testosterone concentrations (Pache et al., 1993). Another study using conventional 2D ultrasonography scanning demonstrated a significant correlation between ovarian volume and serum androstenedione concentrations in PCOS patients (Puzigaca et al., 1991). These studies sustain the general opinion that ovarian stromal changes and total ovarian volume enlargement associated with chronic hyperandrogenic anovulation are distinctive features of PCOS. However, the use of 3D ultrasound in our study suggests that total ovarian volume, total follicle number and follicular volume are the most important ultrasound features.

Previous evidence (van Hooff et al., 1999) has suggested that blood sampling in the menstrual phase and its relation to progesterone administration in women with PCOS may underestimate any endocrine changes. This may be the reason why some studies have shown no relationship between ultrasound findings and biochemical indices. However, in this study a relationship was demonstrated—although this may have been greater had the sampling been performed in the specific oligomenorrheic phase.

It has been reported that 3D ultrasonography is a system with a high degree of reproducibility and significantly increased precision compared with conventional 2D ultrasound volume measurements (Kyei-Mensah et al., 1996a,b). An advantage of using a 3D ultrasound scan is its ability to measure follicular volume accurately, which may be subtracted from the total ovarian volume in order to estimate stromal volume more accurately (Wu et al., 1998). Using a conventional 2D ultrasound scan, ultrasonography assessment of women with PCOS is limited to measurement of total ovarian volume only (Balen et al., 1995), because this system has no facility for the visualization of the many pre-antral follicles simultaneously in three planes. Therefore, the additional measurements of follicular and stromal volume using computerized 3D ultrasonography improve the accuracy and reproducibility of measurement of the ultrasound features of PCOS.

Although ovarian stroma is still important in the pathophysiology of PCOS (White et al., 1995; Gilling-Smith et al., 1997), 3D assessment of the ultrasound features traditionally used in the diagnosis of PCOS suggests that total ovarian volume and the total pre-antral follicle number and follicular volume are more important. The implication is that it is the follicular volume which is the important component of the total volume, rather than the stromal volume.

The different findings in our prospective observational study compared with those of other studies are unlikely to be due to the fact that the women had CC-resistant PCOS. A prospective study performed in 22 infertile women has demonstrated that there is no difference in the stromal index and ovarian volume between CC-resistant and CC-sensitive PCOS groups (Al-Took et al., 1999). Therefore, these differences are most likely to be as a result of the more accurate determination of stromal volume by 3D rather than 2D ultrasound scanning.

In conclusion, this is the first report showing that ovarian stromal volume, as assessed by 3D ultrasonography, does not correlate with biochemical indices of PCOS. However, the total ovarian volume, total pre-antral follicular volume and pre-antral follicle number do correlate with these indices.

References


Ovarian enlargement as a possible marker of androgen activity in polycystic
Shoham, Z., Jacobs, H.S. and Insler, V. (1993) Luteinizing hormone: its role,
mechanism of action, and detrimental effects when hypersecreted during
the follicular phase. Fertil. Steril., 59, 1153–1161.
Ultrasound., 9, 219–222.
van der Westhuizen, S. and van der Spuy Z.M. (1996) Ovarian morphology
as a predictor of hormonal values in polycystic ovary syndrome. Ultrasound
Variation of luteinizing hormone and androgens in oligomenorrhoea and its
implications for the study of polycystic ovary syndrome. Hum. Reprod.,
14, 1684–1689.
Gonadotrophin and gonadal steroid response to a single dose of a long-acting
agonist of gonadotrophin-releasing hormone in ovulatory and anovulatory
women with polycystic ovary syndrome. Clin. Endocrinol. (Oxf.), 42,
475–481.
role of three-dimensional ultrasonographic images in ovarian measurement.
Fertil. Steril., 69, 1152–1153.
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